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OFFICE OF PREVENTION, PESTICIDE AND TOXIC SUBSTANCES

MEMORANDUM

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SUBJECT: **Triadimefon: Human Health Risk Assessment to Support Reinstatement of Use on Residential Turf.**

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Introduction

Bayer Environmental Science is requesting that the Agency reinstate registration for use on residential turfgrass for seven products containing triadimefon. This memorandum addresses the revised residential and aggregate risk assessment based on removal of the previously retained FQPA factor and an updated point of departure for residential scenarios.

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1.0 Executive Summary

Background

An assessment of the human health risks associated with triadimefon, a fungicide used on turf, was completed by the Health Effects Division (HED) on November 23, 2005, in order to support the reregistration eligibility decision (RED). This risk assessment was slightly revised, and reissued on February 9, 2006 (R. Griffin, D326678). The 2/9/06 assessment indicated risks above target levels for: 1) acute dietary exposure from food (only) uses; 2) acute dietary exposure from drinking water (only); 3) exposure due to use on residential turf; and 4) worker exposure associated with some high-exposure scenarios. As a result of this assessment, all residential and commercial uses for turf, as well as most agricultural uses were cancelled. In response to the registrant Bayer Environmental Science's agreement to voluntarily cancel all food uses, except for pre-plant and post-harvest use on pineapples, HED performed revised aggregate (food + water) analyses presented in the document *Triadimefon & Triadimenol: Aggregate Acute, Chronic, and Short-Term Risk Assessments Reflecting July, 2006 Risk Mitigation in Response to the Phase 4 Triadimefon RED* (D331455). Triadimenol is a metabolite of triadimefon, but is also an active ingredient used for seed treatment only. The same toxicity studies, endpoints and doses for risk assessment were used for triadimefon and triadimenol, and therefore aggregate risk assessments for triadimefon also address exposure from triadimenol. The 7/2006 risk assessment used the revised aggregation estimates of the triadimefon and triadimenol residues resulting from the metabolism of triadimefon as well as the use of triadimenol as an active ingredient. During reregistration, HED determined that a developmental neurotoxicity (DNT) study should be submitted, and retained a 10X database uncertainty factor (UFDB) pending receipt of the study.

Current Action

Bayer Environmental Science has submitted the DNT study and is now requesting the Agency reinstate residential uses on turfgrass for seven products, including both granules and liquids, for use by professionals or homeowners in residential settings. In support of the proposed labels and uses, Bayer Environmental Science has provided the following: 1) a developmental neurotoxicity study 2) a turf transferable residue (TTR) study, and 3) a reduced application rate for residential turf products (relative to the rates first assessed for the RED). The purpose of this memo is to provide a revised residential and aggregate exposure assessment to determine if the residential turf use can be reinstated.

Hazard Characterization

For detailed information, please refer to the reregistration eligibility decision document (RED) *Triadimefon. Preliminary Human Health Risk Assessment* (D326678; Richard Griffin, February 9, 2006).

The toxicology database is complete, with the exception of an immunotoxicity study. Triadimefon is a neurotoxic, triazole fungicide pesticide. The mode of toxic action involves blocking the re-uptake of dopamine leading to increased motor activity and hyperactivity in rodents. A developmental neurotoxicity (DNT) study was not available at the time of the RED. Therefore, a 10X safety factor was retained as a database uncertainty factor to protect for potential developmental neurotoxicity. Since the last risk assessment, an acceptable/nonguideline DNT study has been reviewed and considered for endpoint selection.

As part of the revised 40 CFR Part 158 (12/2007), an immunotoxicity study is included as part of the data requirements for registration of a pesticide (food and non-food uses). This is a data gap for triadimefon, and the study must be submitted to support ongoing registration of products containing triadimefon. However, there were no indications of immunotoxicity in the triadimefon toxicology database. HED does not believe the submission of the required immunotoxicity study will result in a lower point of departure than those currently selected for risk assessment Therefore, a database uncertainty factor is not needed to account for the lack of the immunotoxicity study. Furthermore, with the submission of the required DNT study, there are no residual concerns for pre- and/or post-natal toxicity. There was no evidence of susceptibility in the study, and no concern for developmental toxicity. Consequently, the risk assessment team concluded the FQPA safety factor should be reduced to 1X. Endpoint and dose selections for dietary, occupational, and non-occupational exposure scenarios are the same as those used in the 2006 human health risk assessment for the RED; however, for childrens' exposures, the level of concern (LOC) is reduced from 1000 to 100 based on the revised combined uncertainty factors.

The short-term dermal risk assessment for triadimefon is based on increased activity and reactivity observed in a dermal study with a NOAEL of 300 mg/kg/day and LOAEL of 1000 mg/kg/day. The short-term inhalation risk assessment for triadimefon is based on hyperactivity observed in an oral neurotoxicity study with a NOAEL of 3.4 mg/kg/day and LOAEL of 54.6 mg/kg/day. Long-term exposure to triadimefon is not expected for currently registered uses, and is not expected for the proposed uses on turf. HED's level of concern (LOC) for non-occupational (residential) triadimefon dermal and inhalation exposure is a Margin of Exposure (MOE) of 100, based on a 10X uncertainty factor for interspecies extrapolation and a 10X factor for intraspecies variability. The dermal endpoint was selected from a dermal study; therefore, no dermal absorption adjustment is needed. The inhalation endpoint was selected from an oral neurotoxicity study, and 100 percent inhalation absorption (relative to oral absorption) is assumed. The dermal and inhalation margins of exposure were combined for the triadimefon risk assessment because the endpoints for the dermal and inhalation routes of exposure, i.e., neurotoxicity, are the same.

Although triadimefon was classified as a "Possible Human Carcinogen" a cancer potency factor was not determined for quantitative cancer risk assessment; rather, the Cancer Peer Review Committee indicated that risk assessments conducted using the chronic reference dose would be protective of potential cancer risk for triadimefon. This conclusion was based on the determination that the thyroid adenomas were borderline in terms of statistical significance and, despite the presence of hepatocellular adenomas in both sexes of mice, all of the tumors associated with the active ingredient were benign. Finally, triadimefon is not a mutagen based on the submitted studies.

Occupational Exposure

Occupational exposures associated with triadimefon use were previously assessed as part of the Reregistration Eligibility Decision (RED) document for triadimefon completed by the Agency (S. Recore; D314814, D315040; June 30, 2006). The results of the occupational exposure assessment indicate that risks are not of concern (MOE >100).

Residential Exposure

Triadimefon is a systemic fungicide formulated as an emulsifiable concentrate, wettable powder, water soluble packet, water dispersible granule (dry flowable), and granular. It may be applied in residential settings using a hose-end sprayer or push-type spreader. There is potential for both short- and

intermediate-term non-occupational exposures to triadimefon during mixing, loading, application and postapplication activities. Since the short- and intermediate-term exposure durations rely on the same toxicity study and intermediate-term exposures would be lower, the short-term assessment is also protective for intermediate-term exposures. Chronic residential exposure is not expected for the proposed (or existing) use patterns associated with triadimefon.

No chemical-specific data for assessing handler exposures were submitted to the Agency in support of the proposed uses; therefore, HED used surrogate data from the Pesticide Handlers Exposure Data Base (PHED) Version 1.1, the Outdoor Residential Exposure Task Force (ORETF), and the Residential Standards Operating Procedures. The standard values established by the Health Effects Division (HED) Science Advisory Council for Exposure (ExpoSAC) were used for amount handled per day and body weight. For assessing postapplication dermal exposures for all populations, MOEs were calculated separately using chemical specific TTR data and default values. Postapplication oral exposures for toddlers were calculated using default assumptions.

The results of the residential handler and adult postapplication exposure assessment indicate that risks are not of concern (MOE > 100). The toddler combined postapplication MOE (dermal + incidental oral ingestion) is 88 (using HED default values) or 96 (using TTR Data), and based on the characterization presented below for the endpoint for dietary and incidental oral exposures these MOEs are recognized as conservative risk estimates.

HED identified a risk of concern for toddlers' ingestion of granules following application of granular formulations to residential lawns or recreational turf. Using standard assumptions for granular ingestion, HED calculated an MOE of 26 based on the dose and endpoint selected for acute dietary exposure. However, the true MOE may be as much as 3-fold higher, near 78, when the conservative nature of the dose selected for risk assessment is taken into consideration. HED's concern for incidental ingestion of granules is further reduced because proposed labels recommend watering lawns/turf immediately after application of granular products, and due to additional information provided by Bayer with respect to the composition of the granules as well as the size and appearance of the granules on turf. With this additional information, HED concluded that children would be unlikely to consume the granules, and therefore there is no concern for risk from granular ingestion.

Aggregate Exposure

Acute and chronic aggregate risks result from exposure to triadimefon residues in food and drinking water, and are equivalent to those discussed in the 7/2006 dietary risk assessment (D331455). However, HED notes that since the 10X FQPA factor has been reduced to 1X with the submission of the DNT study, the acute and chronic population adjusted doses (aPAD) have increased by a factor of 10, and therefore the current risks are much lower than those cited in the 2006 document and are not of concern.

Short-term exposures (1 to 30 days of continuous exposure) may occur as a result of entering outdoor areas previously treated with a triadimefon residential turf product. Exposures related to outdoor activities have been combined with chronic dietary (food + water) exposure estimates discussed in the 7/2006 dietary exposure memo to determine short-term aggregate exposure and risk. For assessing aggregate risks for adults and children, MOEs were calculated separately using chemical specific TTR data for the dermal route and default values for the incidental oral route.

Although the short-term aggregate MOEs for children are above the level of concern (MOEs=92-94 using TTR data), HED considers these as conservative risk estimates based on the current hazard characterization. Considering the results of all the rodent studies (i.e., observed effects and dose spans), there is sufficient evidence to support an endpoint for dietary and incidental oral exposure scenarios as much as three times higher than the 3.4 mg/kg/day used in the current human health risk assessment. In addition to the hazard considerations, the drinking water concentrations used in the current dietary assessment have not been adjusted to account for the lower application rate to turf. Therefore, based on the conservativeness built into the toxicity endpoints and the weight of evidence, HED believes that the short-term aggregate risks for children are not of concern. The risk estimates for short-term exposures are also protective of intermediate-term exposures due to the same toxicity endpoints and NOAELs for both durations of exposure.

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED) and Occupational Residential Exposure Task Force (ORETF), have been determined to require a review of their ethical conduct, have received that review, and have been determined to be ethical.

Recommendations

Based on the current risk assessment, HED recommends:

1. **The proposed labels should be revised to ensure that the maximum application rates are explicitly presented (when applicable) and that the appropriate application equipment for homeowner use is listed.**
2. **Provided the labels are revised as noted above, HED has no objection to reinstating use on residential turf at 2.0 lb ai per acre.**

2.0 Use Profile

A summary of the proposed residential turf use patterns and end-products is presented in Table 1.

Table 1. Summary of Directions for Use of Triadimefon.

Application. Timing, Type, and Equip.	Trade Name; Formulation [EPA File Symbol No.]	Max Single Application. Rate (lb ai/A)
Turf. Max annual application rate: 5.4 lb ai/A. Min retreatment interval: 14 days.	Bayleton® 50; WSP [432-1360]	2.0 lb ai/A (residential use)
Turf. Max annual application rate: 5.4 lb ai/A. Min retreatment interval: 14 days.	Bayleton® 50; WDG [432-1367]	2.0 lb ai/A (residential use)
Turf. Max annual application rate: 5.4 lb ai/A. Min retreatment interval: 14 days.	Bayleton® FLO; [432-1445]	2.0 lb ai/A (residential use)
Turf. Max annual application rate: 5.4 lb ai/A. Min retreatment interval: 14 days.	Bayleton 1% Granular; [432-1336]	2.0 lb ai/A (residential use)
Turf. Max annual application rate: 5.4 lb ai/A. Min retreatment interval: 14 days.	Bayleton® 1 Granular; [72155-xx]	1.3 lb ai/A (residential use)
Turf. RTU. 1 quart treats up to 5,000 ft^2. This product could be reapplied as needed. Min Retreatment interval: 30 days.	Bayleton 3.62% Concentrate; Liquid; [72155-xx]	0.63 lb ai/A (residential use)

3.0 Hazard Characterization

Hazard Characterization and Assessment

For detailed information, refer to the RED (D326678; Richard Griffin, February 9, 2006). The toxicology database is complete, with the exception of an immunotoxicity study.

The database adequately characterizes triadimefon as having low acute oral, dermal and inhalation toxicity. It is Toxicity Category III for acute dermal and inhalation toxicity and Toxicity Category IV for acute inhalation and acute eye and dermal irritation. The acute toxicity profile for triadimefon is presented in Table 2. Triadimefon is a neurotoxic, triazole fungicide pesticide. The mode of toxic action involves blocking the re-uptake of dopamine which leads to increased motor activity and hyperactivity in rodents. Triadimefon acts as an indirect dopamine agonist by binding to the dopamine transporter and increasing levels of synaptic dopamine. Signs of neurotoxicity include hyperactivity, increased motor activity, rearing, body temperature, habituation, and spatial distribution.

FQPA Safety Factor Considerations

Despite a data gap for the required immunotoxicity study, the toxicology database for triadimefon is adequate to characterize potential pre- and/or post-natal risk for infants and children. Acceptable/guideline studies for developmental toxicity in rats and rabbits, 2-generation reproduction study in rats, and neurotoxicity are available for FQPA assessment. Detailed information on most of these studies is available in the RED (D326678; Richard Griffin, February 9, 2006). The developmental neurotoxicity study was not available for the RED and is therefore characterized in the current assessment.

As described in the RED, based on the ability of triadimefon to interfere with synaptic dopamine levels, and the unknown impact during development, a developmental neurotoxicity study was required. A 10X database uncertainty factor was retained in the absence of a DNT. The Agency has since received and reviewed an acceptable/nonguideline DNT study. Maternal effects were limited to decreases in body weights on gestation day (GD) 13 and lactation day (LD) 0 (%5 each, $p<0.05$) and body weight gain during GD 0-20 (6%, not significant). The maternal LOAEL was 71.3 mg/kg/day and the NOAEL was 23.9 mg/kg/day. The offspring LOAEL, 71.3 mg/kg/day was based on post-weaning clinical signs (deviated snout); decrease in pre-weaning body weights (post-natal day 11, 17, and 21) in both sexes; pre-weaning body weight gain in both sexes; increased amplitude during auditory startle reflex testing in females; and increased number of trials to criterion during the retention phase of the passive avoidance test in females. The offspring NOAEL is 23.9 mg/kg/day.

The DNT study was considered for endpoint selection. However, the previously selected endpoints for dietary, occupational, and non-occupational exposure scenarios were considered to be protective of effects seen in the DNT. Therefore, the toxicological endpoints and doses selected in the RED were retained in the current human health risk assessment.

To determine if an additional uncertainty factor should be retained pending submission of the immunotoxicity study, HED examined the database for evidence that triadimefon targets the immune system. The toxicology database for triadimefon does not show any evidence of treatment-related effects on the immune system, and the overall weight of evidence suggests that this chemical does not directly target the immune system. HED does not believe that conducting a functional immunotoxicity study will result in a lower point of departure (POD) than that currently used for overall risk assessment. Therefore, a database uncertainty factor (UF_{DB}) is not needed to account for the lack of this study. Given that there was no evidence of quantitative or qualitative susceptibility in the database, there are no residual concerns for pre- and/or post-natal toxicity, the risk assessment team concluded the 10X FQPA safety factor should be removed (reduced to 1X), and the level of concern (LOC) for residential uses is decreased from 1000 to 100. Exposure scenarios resulting in MOEs below 100 are of concern to HED.

Endpoint Selection

A summary of the toxicological doses and endpoints is provided in Table 3. Adverse effects were identified at durations of exposure ranging from short-term (up to 30 days) to intermediate-term durations (> 30 days up to 6 months) and long-term durations (> 6 months). However, the acute and subchronic NOAELs were similar, indicating triadimefon has a low potential for accumulation following multiple doses. Therefore, the NOAEL of 3.4 mg/kg/day selected from the subchronic neurotoxicity study at which neurotoxic effects were observed at the LOAEL of 54.6 mg/kg/day is appropriate for both acute and short-term exposure scenarios. Chronic exposure is not expected for the proposed use patterns associated with triadimefon.

Regardless of the route and duration of exposure, the endpoints selected for risk assessment were either hyperactivity or increased activity, which are considered to be neurotoxic effects. The dermal endpoints were selected from a route-specific dermal toxicity study, with a NOAEL of 300 and a LOAEL of 1000 mg/kg/day, at which increased activity and reactivity were observed. For acute and chronic dietary, short- and intermediate-term incidental oral, and short- and intermediate-term inhalation risk assessment, the subchronic oral toxicity study in rats was selected based on hyperactivity observed at 54.6 mg/kg/day with a NOAEL of 3.4 mg/kg/day. For inhalation risk

assessment, a 100% inhalation absorption factor was used to extrapolate from the oral to the inhalation route of exposure.

Although triadimefon was classified as a "Possible Human Carcinogen" a cancer potency factor was not determined for quantitative cancer risk assessment; rather, the Cancer Peer Review Committee indicated that risk assessments conducted using the chronic reference dose would be protective of potential cancer risk for triadimefon. This conclusion was based on the determination that the thyroid adenomas were borderline in terms of statistical significance and, despite the presence of hepatocellular adenomas in both sexes of mice, all of the tumors associated with the active ingredient were benign. Finally, triadimefon is not a mutagen based on the submitted studies.

Table 2. Summary of Acute Toxicity Profile for Triadimefon.

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral - rat	00264276	LD_{50} = 1470 mg/kg (Males) LD_{50} = 1090 mg/kg (Females)	III
870.1200	Acute dermal- rabbit	00264276	LD_{50} >2000 mg/kg	III
870.1300	Acute inhalation - rat	41616002	LC_{50} > 3.570 mg/L	IV
870.2400	Acute eye irritation - rabbit	41782501	Slightly irritating	IV
870.2500	Acute dermal irritation – rabbit	41616004	Not an irritant	IV
870.2600	Skin sensitization - guinea pig	41554001	Sensitizer	NA

Table 3. Summary of Toxicological Doses and Endpoints for Triadimefon in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern (LOC) for Risk Assessment	Study and Toxicological Effects
Acute Dietary (all populations)	NOAEL = 3.4 mg/kg/day UF = 100 Acute RfD = 0.034 mg/kg/day	FQPA SF = 1X aPAD = acute RfD / FQPA SF aPAD = 0.034 mg/kg/day	Subchronic neurotoxicity study in rats. LOAEL = 54.6/68.7 mg/kg/day based largely on hyperactivity.
Chronic Dietary (all populations)	NOAEL = 3.4 mg/kg/day UF = 100 chronic RfD = 0.034 mg/kg/day	FQPA SF = 1X PAD = chronic RfD / FQPA SF cPAD = 0.034 mg/kg/day	Subchronic neurotoxicity study in rats. LOAEL = 54.6/68.7 mg/kg/day based largely on hyperactivity.
Incidental Oral Short-Term (1 - 30 days)	NOAEL = 3.4 mg/kg/day UF = 100	Residential MOE = 100	Subchronic neurotoxicity study in rats. LOAEL = 54.6/68.7 mg/kg/day based largely on hyperactivity.
Incidental Oral Intermediate-Term (1 - 6 months)	NOAEL = 3.4 mg/kg/day UF = 100	Residential MOE = 100	Subchronic neurotoxicity study in rats. LOAEL = 54.6/68.7 mg/kg/day based largely on hyperactivity.
Dermal Short-Term (1 - 30 days)	Dermal NOAEL = 300 mg/kg/day	Residential MOE = 100	21 Day Dermal Toxicity in rabbits. The LOAEL= 1000 mg/kg/day based on increased reactivity and activity in the females.
Dermal Intermediate-Term (1 - 6 months)	Dermal NOAEL = 300 mg/kg/day	Residential MOE = 100	21 Day Dermal Toxicity in rabbits. The LOAEL= 1000 mg/kg/day based on increased reactivity and activity in the females.
Dermal Long-Term (> 6 months)	Not Applicable	Not Applicable	Quantitative risk assessment is not required since no long- term dermal exposure is expected.
Inhalation Short-Term (1 - 30 days)	NOAEL = 3.4 mg/kg/day (Inhalation absorption rate = 100%)	Residential MOE = 100	Subchronic neurotoxicity study in rats. LOAEL = 54.6/68.7 mg/kg/day based largely on hyperactivity.
Inhalation Intermediate-Term (1 - 6 months)	NOAEL = 3.4 mg/kg/day (Inhalation absorption rate = 100%)	Residential MOE = 100	Subchronic neurotoxicity study in rats. LOAEL = 54.6/68.7 mg/kg/day based largely on hyperactivity.
Inhalation Long-Term (> 6 months)	Not Applicable	Not Applicable	Quantitative risk assessment is not required since no long- term exposure is expected.
Cancer (oral, dermal, inhalation)	Classification: Category C "possible human carcinogen" based on statistically significant increase in thyroid adenomas in male Wistar rats and statistically significant increases in hepatocellular adenomas in both sexes of the NMRI mouse.		

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

Table 4. Summary of Toxicological Doses and Endpoints for Triadimefon in Occupational Human Health Risk Assessments.

Exposure Scenario	Dose Used in Risk Assessment, UF	Level of Concern (LOC) for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term and Intermediate-Term (1 - 30 days) (1-month – 6 months)	Dermal NOAEL = 300 mg/kg/day	Occupational MOE = 100	21 Day Dermal Toxicity in rabbits. The LOAEL= 1000 mg/kg/day based on increased reactivity and activity in the females.
Dermal Long-Term (> 6 months)	Not Applicable	Not Applicable	Quantitative risk assessment is not required since no long- term dermal exposure is expected.
Inhalation Short-Term and Intermediate-Term (1 - 30 days) (1-month – 6 months)	NOAEL = 3.4 mg/kg/day (Inhalation absorption rate = 100%)	Occupational MOE = 100	Subchronic neurotoxicity study in rats. LOAEL = 54.6/68.7 mg/kg/day based largely on hyperactivity.
Inhalation Long-Term (> 6 months)	Not Applicable	Not Applicable	Quantitative risk assessment is not required since no long- term exposure is expected.
Cancer (oral, dermal, inhalation)	Classification: Category C "possible human carcinogen" based on statistically significant increase in thyroid adenomas in male Wistar rats and statistically significant increases in hepatocellular adenomas in both sexes of the NMRI mouse.		

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. MOE = margin of exposure. LOC = level of concern.

4.0 Occupational Exposure and Risk

Occupational uses registered for triadimefon were previously assessed as part of the RED for triadimefon completed by the Agency in June, 2006 (S. Recore; D314814, D315040; June 30, 2006).

5.0 Residential/Recreational Exposure and Risk

The registrant, Bayer Environmental Science, is requesting that the Agency reinstate residential uses on turfgrass for the following seven products: Bayleton Technical Fungicide (3125-MO-1), Bayleton 50 Turf and Ornamentals in Water Soluble Packets (432-1360), Bayleton 50 WDG Nursery and Greenhouse Systemic Fungicide (432-1367), Bayleton FLO Turf and Ornamental Fungicide (432-1445), Bayleton 1% Granular Turf and Sod Production Fungicide (432-1336), Bayleton 1 Granular (72155-xx), and Bayleton 3.62% Concentrate Systemic Fungicide (72155-xx). In an effort to register these uses, Bayer Environmental Science has provided the following data and mitigation measures: 1) a developmental neurotoxicity study to address the 10X safety factor, 2) a turf transferable residue (TTR) study, and 3) reduction in application rates (relative to those assessed in the RED) for residential turf products. The purpose of this memo is to provide a revised residential and aggregate exposure assessment incorporating the new data and mitigation measures.

5.1 Residential Handler

Triadimefon is proposed for use on residential turfgrass and recreational sites. The proposed labels allow application by home-owners; therefore, short-term non-occupational handler exposure was evaluated. Since the short- and intermediate-term exposure durations rely on the same toxicity study, this assessment is also protective for intermediate-term handler exposures. HED's Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments, and Recommended Revisions (HED Policy Number 11, revised 22 Feb 2001), were used to assess all residential handler exposure calculations. Data from the ORETF (MRID # 44972201) were used in this assessment in place of PHED handler data for the garden hose-end sprayer scenario, which provided more confidence in the exposure estimate. Residential handler risks are summarized below in Table 5, and are not of concern regardless of the application method.

Residential Handler Exposure and Risk Estimates for Cancer

Although triadimefon was classified as a "Possible Human Carcinogen", the Cancer Peer Review Committee indicated that risk assessments conducted using the chronic reference dose would be protective of potential cancer risk for triadimefon. This risk assessment will be based on the cPAD and the margin of exposure (MOE) approaches only.

Table 5. Margins of Exposure for Triadimefon Residential Handler Risks

Exposure Scenario	Crop or Target	Application Rate[a] (lb ai/gallon)	Area Treated Daily[b]	Unit Exposures[c]		Dose (mg/kg/day)		MOEs		
				Dermal (mg/lb ai)	Inhalation (mg/lb ai)	Dermal	Inhalation	Dermal	Inhalation	Dermal + Inhalation[d]
Mixer/Loader/Applicator										
Mixing/Loading/ Applying Liquid Concentrates with Hose-End Sprayer (Residential ORETF data)	turf (home lawns)	2.0 lb ai/A	0.5 A	11	0.017	0.157	0.00024	1,900	14,000	1,700
Loading/Applying Granulars via Push Type Spreader (ORETF data)	turf	2.0 lb ai/A	0.5 acres	0.67	0.88 (0.00088 mg/lb ai)	0.00957	0.000013	31,000	230,000	27,000
	turf	1.3 lb ai/A	0.5 acres	0.67	0.88 (0.00088 mg/lb ai)	0.00622	0.000008	48,000	430,000	43,000

a. Application rates are the maximum application rates determined from EPA registered labels for triadimefon.
b. Amount handled per day values are HED estimates of acres treated per day based on Exposure SAC SOP #9 "Standard Values for Daily Acres Treated in Agriculture," industry sources, and HED estimates.
c. Baseline attire is long-sleeve shirt, long pants, and no gloves and no respirator.
d. Total MOE = 1 / (1/Dermal MOE + 1/Inhalation MOE)

5.2 Residential Postapplication

HED uses the term "postapplication" to describe exposures to individuals that occur as a result of being in an environment that has been previously treated with a pesticide. Triadimefon can be used in many areas that can be frequented by the general population, including residential areas (e.g., home lawns and gardens). As a result, individuals can be exposed by entering these areas if they have been previously treated.

Residential postapplication exposure via the inhalation route is expected to be negligible; however, dermal exposure is likely for adults and children entering treated lawns. Toddlers may also experience exposure via incidental non-dietary ingestion (i.e., hand-to-mouth, object-to-mouth (turfgrass), and soil ingestion) during postapplication activities on treated turf. The postapplication risk assessment is based on generic assumptions as specified by the Recommended Revisions to the Residential SOPs and recommended approaches by HED's ExpoSAC.

HED considered a number of exposure scenarios for products that can be used in the residential environment representing different segments of the population including toddlers, youth-aged children, and adults. Short-term MOEs were calculated for all scenarios. Since the short- and intermediate-term exposure durations rely on the same toxicity endpoint, this assessment is also protective for intermediate-term postapplication exposures. In residential settings, HED does not use restricted-entry intervals (REIs) or other mitigation approaches to limit postapplication exposures because they are viewed as impractical and not enforceable. As such, risk estimates on the day of application are the key concern.

Residential Postapplication Exposure Scenarios

The populations that were considered in the assessment include:

- Residential Adults: these individuals are members of the general population that are exposed to chemicals by engaging in activities at their residences (e.g., in their lawns or gardens) and also in areas not limited to their residence (e.g., golf courses or parks) previously treated with a pesticide. These kinds of exposures are attributable to a variety of activities and are usually addressed by HED in risk assessments by considering a representative activity as the basis for the exposure calculation.

- Residential Children: children are members of the general population that can also be exposed in their residences (e.g., on lawns and other residential turfgrass areas). Toddlers have been selected as the representative population for turf.

The following postapplication exposure scenarios resulting from lawn treatment were assessed: (1) adult, youth and toddler postapplication dermal exposure, (2) toddlers' incidental ingestion of pesticide residues on lawns from hand-to-mouth transfer, (3) toddlers' object-to-mouth transfer from mouthing of pesticide-treated turfgrass, (4) toddlers' incidental ingestion of soil from pesticide-treated residential areas, and (5) toddlers' incidental ingestion of pesticide granules following application of granular products to lawns.

Data and Assumptions for Residential Postapplication Exposure Scenarios

The assumptions and factors used in the risk calculations are consistent with using the latest HED standard operating procedures and current Agency policy for completing residential exposure assessments (i.e., SOPs for Residential Exposure Assessment). Dermal exposures were assessed two ways: using chemical-specific TTR/Transfer Coefficient values and HED defaults. The values used in this assessment include:

Dermal Exposures

1. TTR Data Approach

- For high-contact activities, TTR values for dermal exposures are from a triadimefon-specific turf transferable residue study (note the study estimated both TTR values and transfer coefficients for adults and 5 year olds).
  - The dermal transfer coefficients (adults: 29,125 cm^2/hr; toddlers (5-year-olds): 12,274 cm^2/hr) calculated in the study were used in place of the default Residential SOP values (adults: 14,500 cm^2/hr; toddlers: 5,200 cm^2/hr) for high contact lawn activities. The TTR study assumed that a typical 5-year-old child weighs 18.7 kilograms. In order to combine incidental oral and dermal risks to toddlers, the incidental oral risks were calculated using the 18.7 kilograms for a 5-year-old child, rather than the usual 15 kilograms for a 3-year-old child, as assumed in the Standard Operating Procedures for Residential Assessments.

2. HED Default Approach

- Five percent (5%) of the application rate is available on day 0 (i.e., 12 hours after application) from turf as transferable residues for dermal exposures.
- Residues dissipate at a rate of 10 percent per day.
- HED default transfer coefficient (presented during the 1999 Agency presentation before the FIFRA Science Advisory Panel) and the transfer coefficient from the triadimefon-specific TTR study were used for high contact dermal exposures on turf.
- HED default transfer coefficients values for short-term dermal exposures are 14,500 cm^2/hr (adults) and 5,200 cm^2/hr (toddlers); and for intermediate-term are 7,300 cm^2/hr (adults) and 2,600 cm^2/hr (toddlers).
- Three year old toddlers are assumed to weigh 15 kilograms (representing an average weight from years one to six for all the default calculations).

Indirect Ingestion Exposures (HED Default only)

- HED default values were used to estimate indirect ingestion exposures and risks.
- Twenty percent (20%) of the application rate has been used to calculate the day-zero residue levels used for assessing risks from object-to-mouth behaviors (a higher percent transfer has been used for object-to-mouth behaviors, because it involves a teething action believed to be more analogous to DFR/leaf wash sample collection where 20

percent is also used).

- On the day of application (day 0), five percent (5%) of the application rate is available for transfer from hand-to-mouth exposures.
- Hand-to-mouth exposures are based on a frequency of 20 events/hour for short-term and 9.5 events/hour for intermediate-term, and a surface area per event of 20 cm^2, representing the palmar surfaces of three fingers.
- Saliva extraction efficiency is 50 percent, meaning that every time the hand goes in the mouth approximately ½ of the residues on the hand are removed.
- Object-to-mouth exposures are based on a 25 cm^2 surface area.
- Soil residues are contained in the top centimeter, and soil density is 0.67 mL/gram.

General Assumptions

- Exposure durations for turfgrass scenarios are estimated to be 2 hours based on information in the Exposure Factors Handbook.
- Dermal and hand-to-mouth are combined to represent an overall risk from exposure to turf, while granular ingestion is considered to be an episodic behavior and is considered separately by HED.
- Three year old toddlers are assumed to weigh 15 kilograms (representing an average weight from years one to six for all the default calculations).
- Adults are assumed to weigh 70 kilograms.
- Youth are assumed to weight 39 kg.
- Postapplication residential risks are based on maximum application rates or values specified in the SOPs for Residential Exposure Assessment.

Evaluation of Potential Exposure Resulting from Contact with Bayleton-Treated Turf (MRID No. 431254-01).

This study was used to assess postapplication exposure and risk from treated turfgrass for high-contact activities. The study provides dermal exposure values, turf transferable residue (TTR) values and dermal transfer factors measured and/or calculated after the application of Bayleton 25 Turf and Ornamental Fungicide to turf. Adult volunteers performed a 20-minute Jazzercise routine on the treated turf, after which dermal exposures were measured. The data were adjusted to obtain surrogate values for 10-year old and 5-year old children. Using the dermal exposures and the TTR values measured, dermal transfer coefficients (cm^2/hr) were obtained for each population. The TTR value (0.502 $\mu g/cm^2$) measured in the study, as well as the calculated dermal transfer coefficients for adults and 5-year olds, were used in the assessment to estimate postapplication exposures from turf due to high contact lawn activities. This value was adjusted for the difference in the study's application rate (2.75 lb ai/acre) and the proposed maximum label application rates.

Residential Postapplication Exposure and Noncancer Risk Estimates

Risks were calculated using the MOE approach. The MOE is a ratio of the toxicological dose for risk assessment (NOAEL) to an estimate of triadimefon exposure to the body. Exposures were calculated by considering the potential sources of exposure (i.e., transferable residues on lawns and golf course

turfgrass) for both the dermal and oral (nondietary ingestion) routes. The algorithms used for each type of calculation are presented below:

Dermal Exposure from Treated Lawns (adult and toddler)

The approach used to calculate the postapplication dermal exposures from contacting treated lawns is:

$ADD = (TTR_0 * ET * TC * DA * CF1) / BW$

Where:

ADD	=	average daily dose (mg/kg/day);
TTR_0	=	turf transferable residue on day "0" ($\mu g/cm^2$);
ET	=	exposure time (2 hr/day);
TC	=	transfer coefficient;
DA	=	dermal absorption factor (100%);
CF1	=	weight unit conversion factor to convert µg units to mg for the daily exposure (0.001 mg/µg); and
BW	=	body weight (kg).

Hand-to-mouth Transfer of Pesticide Residues on Lawns (toddler)

The approach used to calculate the nondietary ingestion exposures that are attributable to hand-to-mouth behavior on treated turf is:

$ADD = (TTR_0 * SA * FQ * ET * SE * CF1) / BW$

Where:

ADD	=	average daily dose (mg/kg/day);
TTR_0	=	turf transferable residue on day "0" ($\mu g/cm^2$);
SA	=	surface area of the hands (20 cm^2/event);
FQ	=	frequency of hand-to-mouth activity (20 events/hr);
ET	=	exposure time (2 hr/day);
SE	=	extraction by saliva (50%);
CF1	=	weight unit conversion factor to convert µg units in the DFR value to mg for the daily exposure (0.001 mg/µg); and
BW	=	body weight (kg).

Object-to-mouth Transfer of Pesticide Residues on Lawns (toddler)

The approach used to calculate exposures attributable to object-to-mouth behavior on treated turf (represented by a child mouthing a handful of turf) is:

$ADD = (TTR_0 * IgR* CF1) / BW$

Where:

ADD	=	average daily dose (mg/kg/day);
TTR_0	=	turf transferable residue on day "0" ($\mu g/cm^2$);
IgR	=	ingestion rate of grass (25 cm^2/day);
CF1	=	weight unit conversion factor to convert the µg of residues on the grass to mg to provide

		units of mg/day (1E-3 mg/μg); and
BW	=	body weight (kg).

Incidental Ingestion of Soil from Pesticide-Treated Residential Areas (toddler)

The approach used to calculate exposures that are attributable to soil ingestion is:

$ADD = (SR_0 * IgR * CF1) / BW$

Where:

ADD	=	average daily dose (mg/kg/day);
SR_0	=	soil residue on day "0" (0.0022 μg/g);
IgR	=	ingestion rate of soil (100 mg/day);
CF1	=	weight unit conversion factor to convert the ug of residues on the soil to grams to provide units of mg/day (1E-6 g/μg); and
BW	=	body weight (kg).

$SRt = TTR_t * F * CF2$

Where:

TTR_0	=	turf transferable residue on day "0" ($\mu g/cm^2$);
F	=	fraction of ai available in uppermost cm of soil (100%/cm); and
CF2	=	volume to weight unit conversion factor to convert the volume units (cm^3) to weight units for the SR value (U.S. EPA, 1992) (0.67 cm^3/g soil).

Incidental Ingestion of Granules from Pesticide-Treated Residential Areas (toddler)

The standard approach used to calculate exposures that are attributable to granule ingestion is:

$ADD = (IgR * F * CF1)/BW$

Where:

ADD	=	average daily dose (mg/kg/day);
IgR	=	ingestion rate of granules (0.2 g/day);
F	=	fraction of ai in dry formulation (unitless);
CF1	=	weight unit conversion factor to convert the g units in the ingestion rate value to mg for the daily exposure (1000 mg/g); and
BW	=	body weight (kg).

The Residential SOPs recommend using an ingestion rate of granules (IgR) of 0.3 g/day, which is based on an application rate of 150 lbs granular product per ½ acre. However, the ingestion rate can be scaled based on the label-recommended application rate. For triadimefon granular products, the proposed application rate is 100 lbs product per ½ acre, and therefore HED used an IgR of 0.2 g/day (i.e., 0.3 g/day x 100/150).

Dermal Exposure from Golfing on Treated Golf Course Turf (adult)

The approach used to calculate the dermal exposures that are attributable to exposure from contacting treated golf course turf is:

$ADD = (DFR_0 * ET * TC * CF1) / BW$

Where:

ADD	=	average daily dose (mg/kg/day);
DFR_0	=	dislodgeable foliar residue on day "0" ($\mu g/cm^2$);
ET	=	exposure time (4 hr/day);
TC	=	transfer coefficient (500 cm^2/hr);
CF1	=	weight unit conversion factor to convert ug units to mg for the daily exposure (0.001 mg/ug)
BW	=	body weight (kg).

Residential Postapplication Risk Summary

Adults

Tables 6 and 7 present the postapplication MOE values calculated for adults after lawn applications of triadimefon. For the residential adult scenarios, short- and intermediate-term MOEs are >100 on the day of application for all scenarios and are not of concern to HED.

Youth-aged children (10 to 12 years old)

Youths were considered for residential turf/mowing scenario. MOEs for these youths were >100 as shown in Tables 6 and 7.

Toddler (3 year old)

Risks (MOEs) to toddlers were calculated for postapplication exposure following the application of triadimefon to home lawns. All dermal (turf/high contact activities) MOEs were >100; oral MOEs were >100 for hand-to-mouth activities, object-to-mouth activities, and soil ingestion. The oral MOEs from hand-to-mouth activity on treated turf range from 114 to 380, which are not of concern.

The exposure estimates are based on some upper-percentile (i.e., maximum application rate, initial amount of transferable residue and duration of exposure) and some central tendency (i.e., surface area and body weight) assumptions. The uncertainties associated with this assessment stem from the use of an assumed amount of pesticide available from turf, and assumptions regarding transfer of chemical residues and hand-to mouth activity.

Exposure due to incidental ingestion of granules following application of granular products to turf results in an MOE of 26, based on the following calculation:

Absorbed Dose = [(0.2 gram granules/day)(0.01 gram ai/gram granule)(1000 mg ai/gram ai)]/15 kg

= 0.133 mg ai/kg/day

MOE = NOAEL/Absorbed Dose = 3.4/0.133 = 26

Off Target Non-Occupational Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for triadimefon. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.
Note that, as indicated in this assessment, triadimefon is directly applied to residential turf and does not result in exposures of concern for the individual scenarios (i.e., oral, dermal). It is unlikely that the potential for risk of exposure to spray drift from previously agricultural registered uses would be higher than that estimated for contact with treated turf.

NOTE: All the MOEs calculated in Tables 6-11 represent the risks from short-term exposures. Since the short- and intermediate-term exposure durations rely on the same toxicity endpoints and NOAELs, these assessments are also protective for intermediate-term postapplication exposures.

Table 6. Dermal Exposure from Treated Lawns and Turf using TTR data

Exposure Scenario	Formulation	Age Group Exposed	Application Rate (lb ai/acre)	TTR Study Application Rate (lb ai/acre)	TTR ($\mu g/cm^2$) on Day 0	TTR ($\mu g/cm^2$) (normalized)	Hours of Exposure	Transfer Coefficient (cm^2/hr)	Absorbed Dermal Dose[a] (mg/kg/day)	Dermal MOE
High Contact Lawn Activities	Spray/Granular	Adult	2.0	2.75	0.502	0.365	2	29,128	0.304	990
	Spray/Granular	Toddler	2.0			0.365		12,274	0.479	**626**
Mowing Turf	Spray/Granular	Adult	2.0	2.75	0.502	0.365	2	500	0.0052	58,000
	Spray/Granular	Youths (10-12 yrs)	2.0			0.365			0.0093	32,000
Golfer	Spray/Granular	Adult	2.0	2.75	0.502	0.365	4	500	0.01043	29,000

Dermal Dose (mg/kg/day) = $(TTR_{norm} * ET * TC * CF1) / BW$

TTR_{norm} = normalized turf transferable residue ($\mu g/cm^2$);
ET = exposure time (2 or 4 hr/day);
TC = transfer coefficient;
CF1 = weight unit conversion factor to convert µg units to mg for the daily exposure (0.001 mg/µg);
BW = body weight (70 kg for adults, 39.1 kg for youth and 18.7 kg for toddlers).

$TTR_{norm} = (TTR_{day\ 0} / TTR_{study\ AR}) * AR$

$TTR_{day\ 0}$ = turf transferable residue on day "0" ($\mu g/cm^2$) from study;
$TTR_{study\ AR}$ = application from turf transferable residue study (lb ai/acre);
AR = application rate from label (lb ai/acre).

Dermal MOE = NOAEL (300 mg/kg/day)/ Absorbed Dermal Dose (mg/kg/day)

Table 7. Dermal Exposure from Treated Lawns and Turf using Default Assumptions								
Exposure Scenario	**Formulation**	**Age Group Exposed**	**Application Rate (lb ai/acre)**	**Default transferable residue (%)**	**Hours of Exposure**	**Transfer Coefficient (cm2/hr)**	**Absorbed Dermal Dose (mg/kg/day)**	**Dermal MOE**
Short-term								
High Contact Lawn Activities	Spray/Granular	Adult	2.0	5%	2	14,500	0.464	**646**
	Spray/Granular	Toddler	2.0			5,200	0.777	**386**
Mowing Turf	Spray/Granular	Adult	2.0	5%	2	3,400	0.109	2,800
	Spray/Granular	Youths (10-12 yrs)	2.0			3,400	0.19	1,600
Golfer	Spray/Granular	Adult	2.0	5%	4	500	0.032	9,400

Dermal Dose (mg/kg/day) = $(TTR_0 * ET * TC * CF1 * CF2) / BW$

TTR_0 = turf residue on day "0" ($\mu g/cm^2$);
ET = exposure time (2 or 4 hr/day);
TC = transfer coefficient;
CF1 = weight unit conversion factor to convert µg units to mg for the daily exposure (0.001 mg/µg);
BW = body weight (70 kg for adults, 39.1 kg for youth and 15 kg for toddlers).

$TTR_0 = AR * F * (1-D)^t * CF2 * CF3 = 2.0 \times 0.05 \times 11.2 = 1.12\ \mu g/cm^2$

TTR_0 = turf residue on day "0" ($\mu g/cm^2$);
AR = application rate (lb ai/acre);
F = fraction of ai available on turf (0.05; unitless);
D = fraction of residue that dissipates daily (0.1; unitless);
t = postapplication day on which exposure is being assessed ("day 0");
CF2 = weight unit conversion factor to convert the lbs ai in the application rate to ug for the TTR value (4.54E8 µg/lb);
CF3 = area unit conversion factor to convert the surface area units (A) in the application rate to cm2 for the TTR value (2.47E-8 acre/cm^2).

Dermal MOE = NOAEL (300 mg/kg/day)/ Absorbed Dermal Dose (mg/kg/day)

Table 8. Oral Exposure from Hand-to-Mouth Activity on Triadimefon Treated Turf									
Exposure Scenario	**Application Rate (lb ai/acre)**	**Fraction of ai Transferable from the Foliage**	**Surface area of hands (cm^2)**	**Exposure Frequency (events/hr)**	**Saliva Extraction Factor**	**Exposure Time (hrs/day)**	**Body Weight (kg)**	**Average Daily Oral Dose[a] (mg/kg/day)**	**Incidental Oral MOE**
Short-term									
Spray									
Hand to Mouth (turf)	2.0	0.05	20	20	50%	2	15	0.0299	**114**
Granular									
Hand to Mouth (turf)	2.0	0.05	20	20	50%	2	15	0.0299	**114**
	1.3							0.019	180

Oral Dose (mg/kg/day) = (TTR_0 * SA * FQ * ET * SE * CF1) / BW

TTR_0 = turf transferable residue on day "0" (µg/cm^2);
SA = surface area of the hands (20 cm^2/event);
FQ = frequency of hand-to-mouth activity (20 events/hr or 9.5 events/hr);
ET = exposure time (2 hr/day);
SE = extraction by saliva (50%);
CF1 = weight unit conversion factor to convert µg units to mg for the daily exposure (0.001 mg/µg);
BW = body weight (15 kg).

TTR_0 = AR * F * (1-D)t * CF2 * CF3 = 2.0 x 0.05 x 11.2 = 1.12 µg/cm^2

TTR_0 = turf residue on day "0" (µg/cm^2);
AR = application rate (lb ai/acre);
F = fraction of ai available on turf (unitless);
D = fraction of residue that dissipates daily (0.1; unitless);
t = postapplication day on which exposure is being assessed ("day 0");
CF2 = weight unit conversion factor to convert the lbs ai in the application rate to ug for the TTR value (4.54E8 µg/lb);
CF3 = area unit conversion factor to convert the surface area units (A) in the application rate to cm2 for the TTR value (2.47E-8 acre/cm^2).

Oral MOE = NOAEL (3.4 mg/kg/day)/ Absorbed Dermal Dose (mg/kg/day)

Table 9. Oral Exposure from Object-to-Mouth Activity on Triadimefon Treated Turf						
Exposure Scenario	**Application Rate (lb ai/acre)**	**Fraction of ai Transferable from the Foliage**	**Surface area of turf mouthed (cm^2)**	**Body Weight (kg)**	**Average Daily Oral Dose[a] (mg/kg/day)**	**Incidental Oral MOE**
Short-term						
Spray						
Object to Mouth (turf)	2.0	20%	25	15	0.0075	450
Granular						
Object to Mouth (turf)	2.0	20%	25	15	0.0075	450
	1.3				0.005	680

Oral Dose (mg/kg/day) = (TTR_0 * IgR* CF1) / BW

TTR0 = turf transferable residue on day "0" (µg/cm^2);
IgR = ingestion rate of grass (25 cm^2/day);
CF1 = weight unit conversion factor to convert the µg of residues on the grass to mg to provide units of mg/day (0.001 mg/µg);
BW = body weight (15 kg).

TTR_0 = AR * F * (1-D)t * CF2 * CF3 = 2.0 x 0.2 x 11.2 = 4.48 µg/cm^2

TTR_0 = turf residue on day "0" (µg/cm^2);
AR = application rate (lb ai/acre);
F = fraction of ai available on turf (unitless);
D = fraction of residue that dissipates daily (0.1; unitless);
t = postapplication day on which exposure is being assessed ("day 0");
CF2 = weight unit conversion factor to convert the lbs ai in the application rate to ug for the TTR value (4.54E8 µg/lb);
CF3 = area unit conversion factor to convert the surface area units (A) in the application rate to cm2 for the TTR value (2.47E-8 acre/cm^2).

Oral MOE = NOAEL (3.4 mg/kg/day)/ Absorbed Dermal Dose (mg/kg/day)

Table 10. Oral Exposure from Soil Ingestion								
Exposure Scenario	**Application Rate**	**% of rate in uppermost 1 cm of soil**	**Ingestion Rate (mg/day)**	**Volume of soil per gram (cm^3/g soil)**	**Soil Residue (µg/mg)**	**Body Weight (kg)**	**Average Daily Dose[a] (mg/kg/day)**	**Incidental Oral MOE**
Short-term								
Spray								
Soil Ingestion	2.0	100%	100	0.67	15.0	15	0.0001	34,000
Granular								
Soil Ingestion	2.0	100%	100	0.67	15.0	15	0.0001	34,000
	1.3				9.7		0.00006	57,000

Oral Dose (mg/kg/day) = (SR_0 * IgR * CF1) / BW

SR_0 = soil residue on day "0" (µg/g);
IgR = ingestion rate of soil (100 mg/day);
CF1 = weight unit conversion factor to convert the µg of residues on the soil to grams to provide units of mg/day (0.000001 g/µg);
BW = body weight (15 kg).

SR_0 = AR * F * CF2 * CF3 * CF4 = 2.0 x 0.67 x 11.2 = 15 µg/g

SR_0 = soil residue on day "0" (µg/g);
AR = application rate (lb ai/A);
F = fraction of ai available in uppermost cm of soil (100%);
CF2 = volume to weight unit conversion factor to convert the volume units (cm^3) to weight units for the SR value (U.S. EPA, 1992) (0.67 cm^3/g soil);
CF3 = conversion rate from pounds active ingredient to micrograms of active ingredient (4.54E+08 µg/lb);
CF4 = conversion rate from acres to cm^2 (2.47E-08 A/cm^2).

Oral MOE = NOAEL (3.4 mg/kg/day)/ Absorbed Dermal Dose (mg/kg/day)

HED combines risk values resulting from separate postapplication exposure scenarios when it is likely they can occur simultaneously based on the use-pattern and the behavior associated with the exposed population. For postapplication exposure to toddlers, HED generally combines the dermal and incidental oral (hand to mouth) exposures, but does not include additional exposure from soil ingestion, or mouthing (i.e., object-to-mouth), since the hand-to-mouth exposure is considered to be a conservative upper-bound estimate of oral postapplication exposure. Granular ingestion is not combined with other pathways of exposure, since it is considered to be episodic in nature. **For the proposed turf uses of triadimefon, the total (dermal + incidental oral) postapplication MOE for toddlers using TTR data resulted in an MOE of 96, and an MOE of 88 when using HED defaults.**

Table 11 presents a summary of the postapplication MOE estimates for adults and children.

The risk for postapplication exposure to toddlers following home lawn applications was calculated as follows:

Total MOE = 1 / [(1/$MOE_{hand\text{-}to\text{-}mouth}$) + (1/$MOE_{dermal}$)]

Table 11. Summary of Short-term Postapplication Exposure and Risk Estimates from Residential Lawns

Scenario and Pathway	TTR_{norm}/TTR_0 ($\mu g/cm^2$) [1]	PDR (mg/kg/day) [2]	MOE [3]	Total MOE [4]
Adult Scenarios (TTR Data)				
(1) High Contact Activities	0.365	0.304	990	990
Adult Scenarios (HED Defaults)				
(1) High Contact Activities	1.12	0.464	646	646
Children's Scenarios (TTR Data for Dermal)				
(1) Dermal	0.365	0.479	626	**96**
(2) Hand-to-Mouth	1.12	0.0299	114	
Children's Scenarios (Default Values)				
(1) Dermal	1.12	0.777	386	**88**
(2) Hand-to-Mouth	1.12	0.0299	114	
Toddlers' Ingestion of Granules				
Oral ingestion of granules	N/A	0.133	**26**	**26**

[1] TTR_0=turf transferable residue on day "0"; TTR_{norm}=turf transferable residue normalized.
[2] PDR=potential dose rate on day "0"
[3] MOE = NOAEL (mg/kg/day)/Dose (mg/kg/day). NOAEL = 3.4 mg/kg/day (oral exposure) and 300 mg/kg/day (dermal.exposure)
[4] Total MOE = 1/ [(1/MOE_{Dermal}) + (1/$MOE_{Hand\text{-}to\text{-}Mouth}$)] for children

6.0 Aggregate Risk Assessments and Risk Characterization

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf.

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intakes by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups. Given the existing and proposed use patterns for triadimefon as well as the health-protective assumptions throughout this risk assessment, it is unlikely that any geographic, ethnic, or socioeconomic population will have increased exposure relative to the standard population subgroups assessed by OPP.

In response to the registrant Bayer CropScience's agreement to voluntarily cancel all food uses, except for pre-plant and post-harvest use on pineapples for triadimefon, HED performed the dietary analyses presented in the document *Triadimefon & Triadimenol: Aggregate Acute, Chronic, and Short-Term Risk Assessments Reflecting July, 2006 Risk Mitigation in Response to the Phase 4 Triadimefon RED* (D331455). This risk assessment uses the revised aggregate (food + water) estimates of triadimefon and triadimenol residues resulting from the metabolism of triadimefon as well as the use of triadimenol as an active ingredient.

6.1 Acute Aggregate Risk

The acute aggregate risks are based on exposure to triadimefon residues in food and drinking water and are equivalent to the risks discussed in the 7/2006 dietary risk assessment (D331455). However, HED notes that since the 10X FQPA factor has been reduced to 1X with the submission of the DNT study, the aPAD has increased from 0.0034 to 0.034 mg/kg/day, and therefore the risks presented in Table 12 are much lower than those cited in the 2006 document.

The acute aggregate dietary exposure estimates from food (triadimefon food (pineapples only) + triadimenol food (bananas and seed treatments)) and drinking water using Florida turf with two applications at 2.7 lb ai/A for drinking water are below HED's level of concern (<100% aPAD) at the 95th percentile of exposure. At the 95th percentile of exposure, risks were estimated to be 3.3% and 9.4% of the aPAD for the U.S. population and all infants (<1 yr), respectively. As shown in Table 12,

potential drinking water exposure is significant when compared with exposure from food, especially for all infants, the most highly exposed population subgroup.

Table 12. Results of Aggregate Acute Dietary Exposure Analysis for Triadimefon and Triadimenol Using DEEM-FCID

Population Subgroup	aPAD (mg/kg/day)	Food Only 95th Percentile Exposure (mg/kg/day)	Food Only 95th Percentile % aPAD	Food + Drinking Water 95th Percentile Exposure (mg/kg/day)	Food + Drinking Water 95th Percentile % aPAD
General U.S. Population	0.034	0.000520	1.5%	0.001106	3.3%
All Infants (< 1 year old)	0.034	0.000828	2.4%	0.003190	9.4%
Children 1-2 years old	0.034	0.001083	3.2%	0.001959	5.8%
Children 3-5 years old	0.034	0.000923	2.7%	0.001765	5.2%
Children 6-12 years old	0.034	0.000668	2.0%	0.001210	3.6%
Youth 13-19 years old	0.034	0.000440	1.3%	0.000859	2.5%
Adults 20-49 years old	0.034	0.000334	<1%	0.000942	2.8%
Adults 50+ years old	0.034	0.000249	<1%	0.000921	2.7%
Females 13-49 year old	0.004	0.000322	<1%	0.000936	2.8%

6.2 Short-Term Aggregate Risk

Short-term exposures (1 to 30 days of continuous exposure) may occur as a result of entering outdoor areas previously treated with a triadimefon residential turf product. Exposures related to outdoor activities (Table 11) have been combined with chronic dietary (food + water) exposure estimates discussed in the 7/2006 dietary exposure memo to determine short-term aggregate exposure and risk. Tables 13 (using TTR data) and 14 (HED Defaults) present the aggregate risks calculated for adults and children associated with lawn applications of triadimefon. As noted previously in this document, the risk estimates risks for short-term exposures are protective of intermediate-term exposures due to the same toxicity endpoints and NOAELs.

Although the short-term aggregate MOEs are above the level of concern for children (MOEs=92-94 using TTR data for dermal exposure and HED defaults for incidental oral exposures), HED considers these as conservative estimates based on the current hazard characterization. Likewise, the incidental ingestion of granules, with an MOE of 26 is also considered to be conservative. The endpoint for dietary and incidental oral exposures is based on hyperactivity observed in the subchronic neurotoxicity study with a NOAEL of 3.4 mg/kg/day and a LOAEL of 54.6 mg/kg/day. The true NOAEL is likely higher based on results from other rodent studies. Several studies, including a DNT, 30-day oral, developmental rat, reproduction studies, and combined chronic/carcinogenicity study, demonstrate NOAELs between 10 and 24 mg/kg/day with LOAELs based on neurotoxicity, liver toxicity, body weight changes and reproductive effects. The acute neurotoxicity study has a lower NOAEL (NOAEL = 2 mg/kg/day with LOAEL = 31.2 mg/kg/day) based upon an appropriate endpoint (neurotoxicity). However, this study was not chosen for endpoint selection because the reviewers determined the NOAEL to be an artifact of dose selection. Based on 1) the number of studies with NOAELs exceeding 3.4 mg/kg/day; 2) similar signs of toxicity at the LOAELs; and 3) the large dose span in the subchronic neurotoxicity study, there is sufficient evidence to support a dose for dietary

and incidental exposure scenarios, as much as three times higher than the 3.4 mg/kg/day used in the current human health risk assessment. Although the NOAEL used for the dermal component of the risk assessment is not impacted by the above characterization, the main driver of the short-term aggregate MOE for children is the oral (hand-to-mouth) component. For the incidental ingestion of granules, the MOE is 26, although the true MOE may be up to 3-fold higher, near 78, when the characterization of the selection of the endpoint and dose for risk assessment is considered. HED's concern for granule ingestion is further reduced based on the label recommendation that lawns be watered after application of granular formulations. At the Agency's request, Bayer Environmental Science provided additional information that decreases HED's concern for risk from potential granule ingestion. First, Bayer stated the granules consist of a wettable powder formulation adhered to a carrier such as clay or corn cob, and are designed to release the active ingredient during watering. In addition, Bayer provided photographs illustrating the small granule size, as well as the granule appearance on turf prior to watering. With the submission of the additional information, HED concludes that due to the relatively small size and neutral/natural coloration of the granules, making them difficult to see on turf or bare ground, and on integration of the granules into turf thatch, the likelihood of a child consuming these granules is extremely low, and the calculated MOE is not of concern.

Based on the inherently conservative toxicity dose and endpoint and the weight of evidence for doses at which neurotoxic effects were seen across a number of studies, HED believes that the short-term aggregate MOEs for children (MOE=92 and 94) are not of concern. In addition to the hazard considerations, HED notes that the estimates of drinking water exposure in the risk assessment are based on an application rate of 2.7 lb ai/A and do not reflect the proposed reduced turf application rate of 2.0 lb ai/A.

Table 13. Estimates of Short-term Aggregate Risks for Triadimefon using TTR Data

Population Subgroup	Margins of Exposure (MOEs)				
	Dietary [1]	Handlers [2]	Dermal [3]	Hand-to-Mouth [4]	Total Aggregate [5]
General U.S. Population	5,600	1,700	990	--	560
All infants	2,100	--	626	114	92
Children 1-2 yrs	3,100	--	626	114	94
Children 3-5 yrs	3,200	--	626	114	94
Children 6-12 yrs	4,700	--	--	--	--
Youth 13-19 yrs	6,800	--	16,000 (golfer)	--	4,800
Adults 20-49 yrs	6,300	1,700	990	--	570
Adults 50+ yrs	6,500	1,700	990	--	570
Females 13-49 yrs	6,400	1,700	990	--	570

[1] Dietary (Food + Water) MOE = Incidental Oral NOAEL (3.4 mg/kg/day) ÷ Chronic Dietary (Food + Water) Exposure.
[2] Handlers Total MOE = 1 / (1/Dermal MOE + 1/Inhalation MOE).
[3] Dermal Postapplication MOE.
[4] Hand-to-mouth is appropriate for infant and children population subgroups only.
[5] Total Aggregate MOE = $1/[(1/MOE_{Dietary}) + (1/MOE_{Dermal}) + (1/MOE_{HtM})]$.

Table 14. Estimates of Short-term Aggregate Risks for Triadimefon using HED Defaults

Population Subgroup	Margins of Exposure (MOEs)				
	Dietary [1]	Handlers [2]	Dermal [3]	Hand-to-Mouth [4]	Total Aggregate [5]
General U.S. Population	5,600	1,700	646	--	430

Table 14. Estimates of Short-term Aggregate Risks for Triadimefon using HED Defaults					
Population Subgroup	Margins of Exposure (MOEs)				
	Dietary [1]	Handlers [2]	Dermal [3]	Hand-to-Mouth [4]	Total Aggregate [5]
All infants	2,100	--	386	114	84
Children 1-2 yrs	3,100	--	386	114	86
Children 3-5 yrs	3,200	--	386	114	86
Children 6-12 yrs	4,700	--	--	--	--
Youth 13-19 yrs	6,800	--	1,600 (mowing)	--	1,300
Adults 20-49 yrs	6,300	1,700	646	--	440
Adults 50+ yrs	6,500	1,700	646	--	440
Females 13-49 yrs	6,400	1,700	646	--	440

[1] Dietary (Food + Water) MOE = Incidental Oral NOAEL (3.4 mg/kg/day) ÷ Chronic Dietary (Food + Water) Exposure
[2] Handlers Total MOE = 1 / (1/Dermal MOE + 1/Inhalation MOE).
[3] Dermal Postapplication MOE.
[4] Hand-to-mouth is appropriate for infant and children population subgroups only.
[5] Total Aggregate MOE = $1/[(1/MOE_{Dietary}) + (1/MOE_{Dermal}) + (1/MOE_{HtM})]$.

6.3 Chronic Aggregate Risk

The chronic aggregate risk in the current assessment is based on exposures to triadimefon residues in food and drinking water, and these exposures are equivalent to those discussed in the 7/2006 document. Chronic risk estimates are below HED's level of concern for all population subgroups, including the most highly exposed population subgroup, all infants. The cPAD and %cPAD values shown below differ from those presented in the 7/2006 document by a factor of 10X, since HED has removed the 10X factor retained for the lack of the DNT. Once again, drinking water exposure is significant relative to exposure from food.

Table 15. Results of Aggregate Chronic Dietary Risk Analysis from (Food Alone) and (Food + Drinking Water-Entire Golf Course) Using DEEM-FCID

Population Subgroup	cPAD (mg/kg/day)	Food Alone		Food + Drinking Water (Entire Course)	
		Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.034	0.000194	<1%	0.000607	1.8%
All Infants (< 1 year old)	0.034	0.000227	<1%	0.001584	4.7%
Children 1-2 years old	0.034	0.000493	1.5%	0.001108	3.3%
Children 3-5 years old	0.034	0.000471	1.4%	0.001047	3.1%
Children 6-12 years old	0.034	0.000323	<1%	0.000720	2.1%
Youth 13-19 years old	0.034	0.000203	<1%	0.000503	1.5%
Adults 20-49 years old	0.034	0.000154	<1%	0.000540	1.6%
Adults 50+ years old	0.034	0.000117	<1%	0.00052	1.5%
Females 13-49 year old	0.034	0.000147	<1%	0.000532	1.6%

6.4 Cancer Risk

Although triadimefon was classified as a "Possible Human Carcinogen" a cancer potency factor was not determined for quantitative cancer risk assessment; rather, the Cancer Peer Review Committee indicated that risk assessments conducted using the chronic reference dose would be protective of potential cancer risk for triadimefon. This conclusion was based on the determination that the thyroid adenomas were borderline in terms of statistical significance and, despite the presence of hepatocellular adenomas in both sexes of mice, all of the tumors associated with the active ingredient were benign. Finally, triadimefon is not a mutagen based on the submitted studies.

7.0 Data Needs and Label Requirements

7.1 Toxicology

As part of the revised 40 CFR Part 158, an immunotoxicity study is included in the data requirements for registration of a pesticide. This applies to both the food and non-food uses of triadimefon. The DCI language for requiring the study is in the appendix:

7.2 Residue Chemistry

There are no data needs for residue chemistry.

7.3 Occupational and Residential Exposure

There are no data needs for occupational and residential exposure assessment. However, HED notes that submission of a new TTR study using the modified California Roller methodology may be useful to refine the oral (hand-to-mouth) exposure estimates.

Based on the current risk assessment, HED recommends:

- **The proposed labels should be revised to ensure that the maximum application rates are explicitly presented (when applicable) and that the appropriate application equipment for homeowner use is listed.**

8.0 References

Triadimefon: Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document (June 30, 2006); S. Recore. D314814 (Occupational); D315040 (Residential).

Triadimefon & Triadimenol: Aggregate Acute, Chronic, and Short-Term Risk Assessments Reflecting July, 2006 Risk Mitigation in Response to the Phase 4 Triadimefon RED (August 1, 2006); Y. Barnes, S. Piper. D331455.

Series 875, Residential and Residential Exposure Test Guidelines: Group B – Postapplication Exposure Monitoring Test Guidelines (V 5.4, Feb. 1998). This document provides general risk assessment guidance and criteria for analysis of residue dissipation data.

Standard Operating Procedures for Residential Exposure Assessment (Dec. 1997). This

document provides the overarching guidance for developing residential risk assessments including scenario development, algorithms, and values for inputs.

Science Advisory Council for Exposure Policy 003.1 (Aug. 2000): Agricultural Transfer Coefficients. This document provides transfer coefficients which have been used to assess exposures in home gardens.

Science Advisory Council for Exposure Policy 12 (Feb. 2001): Recommended Revisions to the Standard Operating Procedures (SOPs) for Residential Exposure Assessment. This document provides additional, revised guidance for completing residential exposure assessments.

Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment (August 1999 Presentation To The FIFRA SAP). This document provides rationale for Agency changes in SOPs.

9.0 Appendixes

Triadimefon Technical : Toxicology Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100a 90-Day oral toxicity (rats)	00048624 Acceptable/guideline 0, 50, 200, 800 and 2000 ppm (0, 2.5, 10, 40 and 100 mg/kg/day)	NOAEL >2000 ppm (100 mg/kg/day) (HDT). Decreased body weight gain and food consumption at 2000 ppm (100 mg/kg/day) was attributed to palatability. The LOAEL was not observed.
870.3100 30-Day oral toxicity (rats)	00048627 Acceptable/guideline 0, 3, 10, or 30 mg/kg/day	NOAEL is 10 mg/kg/day. The LOAEL is 30 mg/kg/day based on increased liver weights.
870.3100b 90-Day oral toxicity (dogs)	00048625 & 00060226 (1974) Acceptable/guideline 0, 150, 600 and 2400 ppm (0, 3.75, 15, and 60mg/kg/day)	NOAEL > 2400 ppm (60mg/kg/day) (HDT). Decreased body weight gain and food consumption at 2400 ppm (60mg/kg/day) was attributed to palatability. The LOAEL was not observed.
870.3200 21-Day dermal toxicity (rats)	42341501 (1992) Acceptable/guideline 0, 100, 300, or 1000 mg/kg bw/day	NOAEL is 300 mg/kg/day. The LOAEL was 1000 mg/kg/day based on increased reactivity and activity in the females.
870.3700a Prenatal developmental in (rats)	00089023 (1981) Acceptable/guideline 0, 10, 25, 50, or 100 mg/kg bw/day	Maternal NOAEL is 10 mg/kg/day and the LOAEL is 25 mg/kg/day based on dose- related increase in both degree and duration of motor activity and/ or depression of maternal weight. Developmental NOAEL is 50 mg/kg/day and the LOAEL is 100 mg/kg/day based on increased incidences of cleft palates; two fetuses from two different litters were found to have cleft palate.
870.3700a Prenatal developmental in (rats)	00149336 & 92188018 (1990) Acceptable/guideline 0, 10, 30, or 90 mg/kg bw/day	Maternal NOAEL is 30 mg/kg/day and the LOAEL is 90 mg/kg/day based on decreased body weight gains. Developmental NOAEL is 30 mg/kg/day. The LOAEL is 90 mg/kg/day based on increased incidences of distended urinary bladders and abnormal ribs (extra ribs and rib buds).
870.3700b Prenatal developmental in (rabbits)	41446201 & 42089601 (1990) Acceptable/guideline 0, 20, 50, or 120mg/kg bw/day	Maternal NOAEL is 50 mg/kg/day and the LOAEL is 120 mg/kg/day based on minor decreases in initial body weight gains, placental weights, and fetal weights and on initial decreased food consumption. Developmental NOAEL is 20 mg/kg/day. The LOAEL is 50 mg/kg/day based on dose-related increases in the incidences of incomplete ossification of the pelvis pubes and anterior and posterior phalanges and irregular spinous processes on the scapula.

870.3800 Reproduction and fertility effects (rats)	00155075, 92188019 & 92188320 (1984) Acceptable/nonguideline 0, 50, or 1800 ppm (0, 2.5, 90 mg/kg/day) The reproductive study in the rat is acceptable/ nonguideline in conjunction with the 3-generation study (MRID 00032541).	Parental/Systemic/ Reproductive toxicity NOAEL was not established because of the equivocal findings on body weights in the F_1 dams and ovary weights in the P dams at 2.5 mg/kg/day. Offspring NOAEL is 2.5 mg/kg/day and the LOAEL is 90 mg/kg/day based on decreased pup weights and viability in the F_1 and F_2 generations and decreased litter size in the F_2 generation. **Based on the combined two studies the Parental systemic/Reproductive toxicity NOAEL is 15 mg/kg/day and the LOAEL is 90 mg/kg/day. The Offspring NOAEL is 15 mg/kg/day and the LOAEL is 90 mg/kg/day.**
870.3800 Reproduction and fertility effects (3 -Gen) (rats)	00032541 (1979) Acceptable/nonguideline 0, 50, 300, or 1800 ppm (0, 2.5, 15, and 90 mg/kg/day) The reproductive study in the rat is acceptable/ nonguideline in conjunction with the multi generation reproduction study (MRID 00155075)	Parental systemic/Reproductive toxicity NOAEL is 15 mg/kg/day and the LOAEL is 90 mg/kg/day based on decreased fertility, body weights, body weight gains, and litter size. Offspring NOAEL and LOAEL is equivocal due to severe reproductive effects (In the F_1 pups, at 90 mg/kg/day, the number of offspring per dam was decreased ($p<0.05$) in the F_{1a} and F_{1b} litters (decr. 20-31%) at post-natal day (PND) 5. At PND 28, viability was decreased ($p<0.01$) in the F_{1a} (90.7% treated vs 97.8% controls) and F_{1b} (56.4% treated vs 84.2% controls) pups. Additionally, body weight gains of the F_{1a} pups were decreased (decr. 10%; $p<0.05$) during lactation). **Based on the combined two studies the Parental systemic/Reproductive toxicity NOAEL is 15 mg/kg/day and the LOAEL is 90 mg/kg/day. The Offspring NOAEL is 15 mg/kg/day and the LOAEL is 90 mg/kg/day.**
870.4100b Chronic toxicity (dogs)	00032539 & 00126261 (1978) Acceptable/guideline 0, 100, or 330, or 1000 ppm (wk 1–54), or 2000 ppm (wk 55-104) M: 0, 3.03, 11.42, 34.70 (wk 1-54) or 68.80 (wk 55-104) mg/kg bw/day F: 0, 3.49, 11.96, 33.67 (wk 1-54) or 60.42 (wk 55-104) mg/kg bw/day	NOAEL is 330 ppm (equivalent to 11.42/11.96 mg/kg/day in males/females). LOAEL is 1000 ppm (equivalent to 34.70/33.67 mg/kg/day in males/females), based on increased alkaline phosphatase levels in both sexes; and decreased food consumption and increased cholesterol in females.

870.4200b Carcinogenicity (mice)	40752101& 40865101 (1986) Acceptable/guideline 0, 50, 300, or 1800 ppm M: 13.5, 76.0, or 550.1 mg/kg/day F: 0, 19.6, 119.4 or 765 mg/kg/day	NOAEL is 50 ppm (equivalent to 13.5/19.6 mg/kg/day in males/females). LOAEL is 300 ppm (equivalent to 76.0/119.4 mg/kg/day in males/females) based on hepatocellular hypertrophy in both sexes; increased liver weights in males; and Kupffer cell proliferation, single cell necrosis and pigment accumulation in the liver of females. At the doses tested, the carcinogenic potential of MEB 6447 in mice is positive. There was a treatment-related increase ($p<=0.05$, study authors) in hepatocellular adenomas. The incidence at the high dose (22% in males and 18% in females) exceeded the concurrent controls (4-6%) and the historical controls (0-18.4% [mean=5.9%] in males and 0-2% [mean=0.3%] in females). A positive trend ($p<0.01$, Agency reviewers, TXR # 007294) in combined liver nodules and hepatocellular adenoma was observed. Furthermore, an increased incidence ($p<0.01$, Agency reviewers, TXR # 007294) of combined liver nodules and hepatocellular adenomas was observed at the high dose in both sexes. Dosing was considered adequate based on hepatotoxicity in both sexes at >=300 ppm; and decreased body weights and body weight gain and increased overall food and water consumption in males at 1800 ppm.
870.4300 Combined Chronic/ Carcinogenicity (rats)	42153901 (1991) Acceptable/guideline 0, 50, 300, or 1800 ppm M: 0, 2.7, 16.4, or 114.0 mg/kg/day F: 0, 3.6, 22.5, or 199.0 mg/kg/day	NOAEL = 16.4/22.5 mg/kg/day in males/females. LOAEL = 114.0/199.0 mg/kg/day in males/females based on increased food consumption in both sexes, incidence of fat in the hepatocytes in both sexes, alanine aminotransferase levels in males, cholesterol levels in females, and absolute and relative (to body) liver weights in females, and decreased body weight and body weight gains in females. At the doses tested, the carcinogenic potential of MEB 6447 is equivocal based on the incidence of thyroid adenomas and cystic hyperplasia in both sexes.
870.5100 Bacterial system	099412 7 099413 acceptable/ guideline	negative
870.5395 Micronucleus assay	00048637 (1977) acceptable/ guideline	negative
870.5450 Cytogenetics dominant lethal assay	00048628 (1976) acceptable/ guideline	negative
870.5550 DNA damage/ Repair	00159343 (1985)	negative

870.6200a acute neurotoxicity screening battery (rats	43495509 (1992) unacceptable/non-guideline 0, 30, 100, 300 mg/kg/day	No definitive NOAEL or LOAEL could be established
870.6200a acute neurotoxicity screening battery (rats)	43936101 (1996) Acceptable/guideline 0, 2, 31.2, 424.4 (females only) and 587.4 (males only)	The NOAEL is 2 mg/kg. The LOAEL for systemic/neurobehavioral findings is 31.2 mg/kg based on clinical signs, FOB, rearing, body temperature, MA, habituation, and spatial distribution in males and females.
870.6200b Subchronic neurotoxicity screening battery (rats)	44153501 (1996) Acceptable/guideline 0,50,800,or 2200 ppm M: 0, 3.4, 54.6 or 149.8 mg/kg/day F: 0,4.3, 68.7, or 189.7 mg/kg/day	NOAEL is 50 ppm (3.4 and 4.3 mg/kg/day, males/females, respectively). LOAEL for neurotoxicity is 800 ppm (54.6 and 68.7 mg/kg/day males/females respectively) based largely on hyperactivity.
870.6300 Developmental Neutoxicity Study in Rats	47377101 (2008) Acceptable/Non-guideline 0, 100, 300, or 800 ppm 0, 8.0, 23.9, 71.3 mg/kg/day	Parental NOAEL is 23.9 mg/kg/day and the LOAEL is 71.3 mg/kg/day based on decreases in body weight on GD 13 and LD 0 and body weight gain during GD 0-20. Offspring NOAEL is 23.9 mg/kg/day and the LOAEL is 71.3 mg/kg/day based on post-weaning clinical signs (deviated snout); decreases in pre-weaning body weight (PND 11, 17, and 21) in both sexes, pre-weaning body weight gain in both sexes; increased peak amplitude during auditory startle reflex testing in females; and increased number of trials to criterion during the retention phase of the avoidance test in females.

870.7485 Metabolism and pharmacokinetics (rats)	42409101(1992) Acceptable/guideline 5 or 50 mg/kg	Radioactivity was not detected in the expired air. The overall recovery of radioactivity was 97-112%. The compound was predominantly excreted (90-98% dose) within 4 days. The excretion profile of the repeated low-dose group was similar to the single low-dose group; however, the excretion profiles were sex-dependent. Over a 4 day-period, recovery in the urine was 24-28% dose in males and 57-66% in females, and recovery in feces was 63-66% in males and 32-40% in females. Thus, based on urinary excretion, absorption was at least 24% dose in males and 57% in females. Less than 1% dose remained in the body 4 days after treatment. Bioaccumulation was not indicated. Tissue residues were highest in the liver (0.088-1.94 ppm) and kidney (0.041-0.38 ppm), and were generally slightly higher in males than in females. RP-HPLC analyses revealed the presence of 15 radioactive components in the urine and 12 in the feces. The 4 major metabolites (1-14% dose, each) in the urine of both sexes were: KWG 0519 acid (2 isomers), KWG 1323-gluc, HO-DeME-KWG 1342 (2 isomers), and DeMe- KWG 132-gluc (2 isomers). The 5 major metabolites (1-15% dose, each) in the feces of both sexes were: KWG 0519 acid (2 isomers), KWG 1323-gluc, KWG 1323, KWG 1342, and KWG 0519 dehydrate. Thus, metabolism of this compound proceeded along several pathways, such as: (i) hydroxylation at the t-butyl moiety and oxidation to the acid or glucuronidation; (ii) reduction of the keto group and subsequent reactions (including sulfate conjugation); and (iii) desmethylation followed by glucuronidation.

870.7485 Metabolism and pharmacokinetics (rats)	00033057(1979) Acceptable/guideline 24.5-25.0 mg/kg	Radioactivity was not detected in the expired air of animals. Over a 7 day-period, recovery in the urine was 29.8% dose in males and 39.9% in females, and recovery in feces was 52.7% in males and 34.5% in females. Thus, based on urinary excretion, absorption was at least 29.8% dose in all animals. Plasma levels of radioactivity were highest 1-2 hours post-dose (2.5-3.2 ppm), and the half-life (calculated by the reviewer) was about 4 hours. Tissue concentrations in males were generally similar to females. The highest concentrations of radioactivity were found in the fat (43.5-45.0 ppm) at 4-8 hours post-dose. Approximately 50% of the radiolabeled compound in the fat of males was unchanged Bayleton and 50% was isomeric forms of the 2-butanol derivative KWG 0519; over 90% was Bayleton in females. In addition, relatively high concentrations of radioactivity were observed in the liver (26.2-28.4 ppm) and skin (21-22 ppm) at 2 hours post-dose. Tissue concentrations were <0.14 ppm at 7 days post-dose. In the urine, the major component of the acidified extract was KWG 0519 acid (6.1-7.7% dose). In the direct extract of urine, 3 minor metabolites were identified: p-chlorophenol, KWG 1323, and KWG 1342 (two isomers). In the direct extract of the feces, KWG 1323, KWG 1342, and KWG 0519 acid (5.7-20.0% dose) were identified. KWG 1323 was the predominant metabolite in the feces of females (12.7% dose), and KWG 0519 acid was the predominant metabolite in the feces of males (20.0% dose). Thus, the major metabolites were the alcohol and acid of Bayleton, which were formed by the sequential hydroxylation and oxidation of the methyl group of the t-butyl chain.

Guideline Number: 870.7800
Study Title: Immunotoxicity

Rationale for Requiring the Data

This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses).

The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies assessing functional immunotoxic endpoints are helpful in fully characterizing a pesticide's potential immunotoxicity. These data will be used in combination with data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies to characterize potential immunotoxic effects.

Practical Utility of the Data

How will the data be used?

These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997).

How could the data impact the Agency's future decision-making?

If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data.

If the Agency does not have this data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

13544

R174607

Chemical Name: Triadimefon

PC Code: 109901
HED File Code: 14000 Risk Reviews
Memo Date: 8/3/2009
File ID: 00000000
Accession #: 000-00-0131

HED Records Reference Center
8/7/2009